

NIH RELAIS Document Delivery

NIH-10005440

NIH -- W1 AM451D

MICHELLE MAHER
NCI/DCPC
6006 Executive Blvd. Suite 321 MSC7058
ROCKVILLE, MD 20892-7058

ATTN:	SUBMITTED:	2001-08-27 15:21:36
PHONE: 301-496-0478	PRINTED:	2001-08-28 11:36:11
FAX: 301-435-8645	REQUEST NO.:	NIH-10005440
E-MAIL:	SENT VIA:	LOAN DOC 4175936

NIH	Fiche to Paper	Journal
TITLE:	AMERICAN JOURNAL OF EPIDEMIOLOGY	
PUBLISHER/PLACE:	School Of Hygiene And Public Health Of J Baltimore Md	
VOLUME/ISSUE/PAGES:	1988 Sep;128(3):467-77 467-477	
DATE:	1988	
AUTHOR OF ARTICLE:	Carter CL; Corle DK; Micozzi MS; Schatzkin A; Taylor PR;	
TITLE OF ARTICLE:	A prospective study of the development of breast cancer in 1	
ISSN:	0002-9262	
OTHER NOS/LETTERS:	Library reports holding volume or year 7910653 3414655	
SOURCE:	PubMed	
CALL NUMBER:	W1 AM451D	
NOTES:	Please email all copy orders	
REQUESTER INFO:	AC956	
DELIVERY:	E-mail: mm130D@nih.gov	
REPLY:	Mail:	

NOTICE: THIS MATERIAL MAY BE PROTECTED BY COPYRIGHT LAW (TITLE 17, U.S. CODE)

-----National-Institutes-of-Health,-Bethesda,-MD-----

A PROSPECTIVE STUDY OF THE DEVELOPMENT OF BREAST CANCER IN 16,692 WOMEN WITH BENIGN BREAST DISEASE

CHRISTINE L. CARTER,¹ DONALD K. CORLE,² MARC S. MICOZZI,³
ARTHUR SCHATZKIN,¹ AND PHILIP R. TAYLOR¹

Carter, C. L. (NCI, Bethesda, MD 20892), D. K. Corle, M. S. Micozzi, A. Schatzkin, and P. R. Taylor. A prospective study of the development of breast cancer in 16,692 women with benign breast disease. *Am J Epidemiol* 1988;128:467-77.

The authors studied the relation between benign breast disease and subsequent breast cancer in 16,692 women with biopsy-diagnosed benign breast disease who had participated in the Breast Cancer Detection Demonstration Project throughout the United States. Women were classified into one of five benign breast disease categories: atypical hyperplasia, proliferative disease without atypia, nonproliferative disease, fibroadenoma, and other benign breast disease. A total of 485 incident cases of breast cancer were identified in the women from August 1973 to February 1986 after a median follow-up period of 8.3 years from the diagnosis of benign breast disease. Age-adjusted incidence rates were calculated for benign breast disease types stratified by family history and calcification status. Relative risk (RR) estimates of breast cancer for women in the five benign breast disease categories, compared with the screened women who did not develop recognizable breast disease (normal subjects), were computed using the proportional hazards model. Results indicated that risk was associated with the degree of epithelial atypia. Over all age groups, women with nonproliferative disease, proliferative disease without atypia, and atypical hyperplasia displayed progressively increasing risks of 1.5, 1.9, and 3.0, respectively, compared with normal subjects, with 95% confidence intervals (CI) exceeding unity. Particularly high risk was seen among women under age 46 years with atypical hyperplasia (RR = 5.7, 95% CI 3.0-10.6). Women with fibroadenoma as the only indication of their benign breast disease had a relative risk of 1.7, with a lower 95% confidence limit of 1.0. No increased risk was seen for women with other benign breast disease. Positive family history (RR = 1.8) and calcification (RR = 1.2) significantly increased a woman's risk proportionately over the risk associated with each benign breast disease subtype. The authors conclude that the risk of developing breast cancer varies by category of benign breast disease and is directly related to the degree of epithelial atypia.

breast diseases; breast neoplasms

Benign breast disease has been considered a risk factor for breast cancer for over 20 years. The specific histologic features of benign breast disease range from cyst for-

Received for publication November 9, 1987, and in final form February 4, 1988.

¹ Cancer Prevention Studies Branch, Division of Cancer Prevention and Control, National Cancer Institute, National Institutes of Health, Blair Building, Room 6A01, 9000 Rockville Pike, Bethesda, MD 20892-4200. (Reprint requests to Dr. Christine L. Carter.)

² Biometry Branch, Division of Cancer Prevention

and Control, National Cancer Institute, National Institutes of Health, Bethesda, MD.

³ Armed Forces Institute of Pathology, Washington, DC.

The authors are indebted to Mary Ellen Baruch for her careful and critical programming analysis, Nina Steele for editorial assistance, Drs. Sylvan Green and Dave Byar for statistical consultation, and Cathy Schairer for technical advice.

mation and stromal fibrosis to epithelial hyperplasia with or without atypia. Early studies (1-7) reported increased risks for breast cancer for women with benign breast disease of approximately two to seven times the risk in women without benign breast disease. In 1968, Veronesi and Pizzocaro (1) reported a twofold increase in the risk of developing breast cancer in over 1,000 patients with histologically confirmed cystic disease after a mean follow-up period of almost nine years. Black et al. (2) and, later, Page et al. (3) found that the increase in risk of breast cancer occurred primarily in patients with epithelial proliferation and particularly in those with atypia. Kodlin et al. (4) found relative risks ranging from 2.4 to 7.0 in a series of almost 3,000 women with biopsy-proven benign breast disease and showed that risk increased as the degree of atypia increased.

More recent studies (8-11) of histologic subclasses of benign breast disease have also shown that the risk for subsequent breast cancer is not uniform. Most of these studies report that the excess risk associated with benign breast disease is approximately two to three times the risk associated with the development of breast cancer in the general population, and that the risk across different benign breast disease histologic subclasses is not uniform.

The Breast Cancer Detection and Demonstration Project collected comprehensive data on a large number of US women screened for breast cancer and followed for over 10 years. This report reflects our evaluation of all biopsy-proven cases of benign breast disease and subsequent development of breast cancer in these women.

MATERIALS AND METHODS

Breast Cancer Detection Demonstration Project

The Breast Cancer Detection Demonstration Project was originally organized as a demonstration project rather than a research study. From 1973-1978, approximately 280,000 women between the ages of

35 and 74 years were recruited to undergo annual screenings, consisting of physical exam and mammography, for breast cancer, at 29 project centers widely distributed throughout the United States in a program sponsored jointly by the American Cancer Society and the National Cancer Institute. Screening phase questionnaires were administered at entry into the project, at each annual screening, and when any surgical procedure was performed. Beginning in 1979, when screening was complete, 64,185 of these women were selected for an additional five years of follow-up as part of a research study to assess the biology and natural history of breast disease. Follow-up women were selected if, by the end of the screening phase, they had been diagnosed with breast cancer or benign breast disease or had received physician recommendation for a breast biopsy but had not undergone one. In addition, an age-, race-, and project-matched sample of women who had completed screening and remained symptom-free were selected as the normal cohort. A follow-up phase baseline interview was given to each of these women to collect data on pertinent demographic information, risk factors, and prevalent disease; annual interviews were then conducted for four subsequent years to capture interval, incident, and morbid events. Further details on the study design of the project have been reported elsewhere (12, 13).

Development of analytic cohort

From a total of 64,185 women selected for the follow-up cohort, 9,620 were excluded because they had been advised to undergo breast biopsy but were never clinically examined. An additional 9,674 were excluded because there was no histologic confirmation for benign breast disease and/or the date of diagnosis was unknown. This left 44,891 women who either had histologic evidence of benign breast disease (19,734) or were free from recognized breast disease (25,157) available for study (table 1). We further excluded women who had breast cancer or cancer in situ at or before the

TABLE 1
*Exclusion criteria for the Breast Cancer Detection
Demonstration Project study population*

Total no. entering follow-up	64,185	
Exclusions†		
Recommended for biopsy but never clinically examined	9,620	
No histologic confirmation and/or unknown date of BBD* diagnosis	9,674	
No. available for study	44,891	
	No. with proven BBD	No. of normal subjects
	19,734	25,157
Further exclusions†		
Cancer at or before proven BBD or missing or unknown date of follow-up phase baseline interview for normal subjects	2,319	1,045
Cancer in situ at or before BBD or at time of follow-up phase baseline interview for normal subjects	403	24
Cancer detected or follow-up period ≤6 months	31	61
Self-reported cancer	18	11
Unknown date of cancer diagnosis	26	11
Unknown family history or age	245	143
Total no. of subjects	16,692	23,862

* BBD, benign breast disease.

† All exclusions occur sequentially.

re recruited to undergo consisting of physical apy, for breast cancer, ers widely distributed ed States in a program the American Cancer ional Cancer Institute. uestionnaires were ad- nto the project, at each nd when any surgical rmed. Beginning in g was complete, 64,185 e selected for an addi- follow-up as part of a ssess the biology and east disease. Follow-up d if, by the end of the y had been diagnosed r benign breast disease ician recommendation ut had not undergone ge-, race-, and project- women who had com- l remained symptom- the normal cohort. A seline interview was women to collect data phic information, risk disease; annual in- onducted for four sub- ure interval, incident, Further details on the project have been re- 13).

of analytic cohort

4,185 women selected hort, 9,620 were ex- had been advised to y but were never clin- additional 9,674 were ere was no histologic gn breast disease and/ is was unknown. This o either had histologic east disease (19,734) gnized breast disease r study (table 1). We men who had breast situ at or before the

diagnosis of benign breast disease, women whose follow-up time or development of breast cancer was within six months of the diagnosis of benign breast disease, women with self-reported cancers, and women with incomplete pathology or risk factor information. After all exclusions, 16,692 benign breast disease cases and 23,862 women who had been screened for five years and were free from recognized breast disease (normal subjects (reference population)) remained and formed the analytic cohort.

Follow-up began in August 1973 and ended in February 1986. For women with benign breast disease, follow-up started six months after the time of their first biopsy.

Median follow-up time for the 16,207 women with benign breast disease who did not develop breast cancer was 8.3 years. For the normal subjects, follow-up started after the five-year screening phase and six months after the follow-up phase baseline interview. Therefore, normal subjects were older at the time of their follow-up phase baseline interview, and median follow-up time for the 23,693 normal subjects who did not develop breast cancer was 3.4 years. Since normal subjects were defined after five years of screening and after all women receiving a diagnosis of benign breast disease or cancer had been reclassified, we were initially concerned that the rates of breast cancer development in the normal subjects might be abnormally low. For comparison of the normal subjects in our study with a well-established sample of US women, we obtained age-specific rates of breast cancer in the Surveillance, Epidemiology, and End Results registries (14).

Histologic classification of benign breast disease

Biopsies were performed on all consenting participants who had abnormalities identified by physical exam or radiography during the screening phase. Pathologists at each study center completed standardized pathology report forms on all women who underwent a biopsy. Diagnostic criteria from these forms were combined into the following five categories: atypical hyperplasia, proliferative disease without atypia, nonproliferative disease, fibroadenoma (alone), and other benign breast disease (see table 2). These categories were created to closely parallel those previously reported (5).

For the 1,467 women who had multiple biopsies performed during the screening phase, only the first biopsy was considered. For the 77 per cent of the cases in whom the qualifying biopsy indicated multiple types of benign breast disease, the category of benign breast disease was defined according to the following hierarchy: atypical hyperplasia, proliferative disease without

TABLE 2

Benign breast disease classifications for the Breast Cancer Detection Demonstration Project study population*

Atypical hyperplasia
Lobular epithelial hyperplasia with atypia
Ductal hyperplasia with atypia
Proliferative disease without atypia
Lobular epithelial hyperplasia, not otherwise specified
Sclerosing adenosis
Ductal papillary hyperplasia
Nonproliferative disease
Ductal ectasia
Papillary apocrine metaplasia
Cyst, epithelial
Cyst, epithelial with apocrine metaplasia
Other benign breast disease
Congenital or developmental anomaly
Acute inflammation or abscess
Chronic inflammation and/or chronic abscess
Granulomatous inflammation
Fat necrosis
Galactocele
Unlisted nonneoplastic lesion
Fibroadenoma (in the presence of histologic features from the other benign breast disease category)
Fibroadenoma (alone)

* Specific conditions were abstracted from pathology record forms completed by project pathologists.

atypia, nonproliferative disease, fibroadenoma, and other benign breast disease.

Other covariates

We examined the influence of age, positive family history, and presence of calcification on the risk of developing breast cancer in each of the five categories of benign breast disease. Age was categorized into three groups to roughly correspond to premenopausal, perimenopausal, and postmenopausal age groups. A positive family history was defined as reported breast cancer in a mother, sister, or daughter. Because data on second-degree relatives (grandmothers, aunts) are often unreliable, we chose to limit the definition of positive family history to affected first-degree relatives (mother, sisters, daughters). Calcification results were based on histologic examination of the biopsy section, as reported by project pathologists.

Case ascertainment

In this report, breast cancer refers to invasive breast carcinoma only. All cases were confirmed either by a pathology report filled out by project pathologists at each of the 29 centers (97.5 per cent) or, when reports were unattainable, by project assignment based on hospital confirmation (2.5 per cent).

In addition, representative slides and copies of pathology reports on all breast cancer cases were sent to a central review group at Vanderbilt University Medical Center, Nashville, Tennessee. Disputed cases were resolved by this group, and review forms were forwarded to the data management center.

Statistical methods

Each woman's follow-up was terminated when she was diagnosed with breast cancer, last responded to a follow-up interview, or died. For purposes of analysis, the latter two events define censoring time.

Crude rates of breast cancer in each of the five benign breast disease groups and in the normal subjects were computed by dividing the number of breast cancers that developed in a given group by the total follow-up time for that group. Age-adjusted rates were computed with coefficient weights derived from a proportional hazards model which included age as a continuous covariate and indicators for family history, calcification, and benign breast disease group, and then by using the coefficient for the age covariate to adjust each group rate to the age midpoint (52.5 years) of our comparison population (Surveillance, Epidemiology, and End Results age group, 50-54 years).

We used proportional hazards techniques to estimate the overall risk of developing breast cancer for different subgroups of our study population. Age at entry biopsy was included in the model as a continuous covariate; separate indicator variables were used to assess the risk associated with family history and calcification status. Normal

certainment

breast cancer refers to carcinoma only. All cases were confirmed by a pathology report from pathologists at each of the study sites (7.5 per cent) or, when not available, by project as a hospital confirmation

representative slides and reports on all breast cancer cases sent to a central review at the University Medical Center, Tennessee. Disputed cases were reviewed by this group, and recommendations forwarded to the data man-

cal methods

Follow-up was terminated for subjects who died, were lost to follow-up, or were interviewed, or for whom, at the time of analysis, the latter was censored time.

Incidence rates of breast cancer in each of the five benign breast disease groups and the normal subjects were computed by dividing the number of breast cancers that occurred in each group by the total person-years in that group. Age-adjusted incidence rates were computed with coefficient of variation from a proportional hazards model including age as a continuous variable and indicators for family history, benign breast disease, and benign breast disease by using the coefficient of variation to adjust each variable to the midpoint (52.5 years) of the study population (Surveillance, Epidemiology, and End Results age

standardized hazards techniques to estimate the overall risk of developing breast cancer in different subgroups of our study population. Age at entry biopsy was included as a continuous covariate and indicator variables were used for family history and calcification status. Normal

subjects served as the reference group. Differences in risk by age, family history, and calcification were evaluated by examining the age-adjusted breast cancer rates within different strata of these variables.

RESULTS

The average age at entry biopsy for the 16,692 women with benign breast disease was 50.9 years; 88 per cent of the women were white and 4 per cent were black. Invasive breast cancer was diagnosed in 485 of these women after a median 8.3 years of follow-up. In the normal cohort, 169 breast cancers were diagnosed after a median 3.4 years of follow-up. In addition, 96 cases of cancer in situ also developed: 68 in women with benign breast disease and 28 in normal subjects.

Table 3 shows the distribution by age, family history, and calcification in the normal cohort and in the five benign breast disease groups. As mentioned above, the normal subjects were slightly older because they had completed five years of screening before their follow-up phase baseline interview. Only 12 per cent of the normal subjects reported a positive family history, whereas 20 per cent of the women with

atypical hyperplasia reported a first-degree relative with breast cancer. Calcification was reported in over 50 per cent of the cases with atypical hyperplasia and in almost 40 per cent of women with proliferative disease without atypia, but in only 14 per cent of women with fibroadenoma or other benign breast disease.

Table 4 shows the crude and age-adjusted rates of breast cancer in the study population. All rates were computed as annual breast cancer incidence rates per 100,000 person-years of observation. Normal women in this cohort had an age-adjusted breast cancer rate of 206.5. This is comparable to the breast cancer incidence rate of 192.2 for women 50-54 years of age who participated in the Surveillance, Epidemiology, and End Results Program between 1973 and 1981 (14). In this study, the age-adjusted breast cancer incidence rates were markedly different depending on the category of benign breast disease. Women with fibroadenoma showed a surprisingly elevated breast cancer incidence rate (334.3) compared with the normal subjects (206.5), whereas the rate in women with other benign breast disease was not substantially increased over that in normal subjects. As

TABLE 3

Descriptive analysis of the Breast Cancer Detection Demonstration Project study population; distribution by age, family history, and calcification status

	Normal subjects		Other BBD*		Fibroadenoma		Nonproliferative disease		PDWA*		Atypical hyperplasia	
	n	%	n	%	n	%	n	%	n	%	n	%
Age (years)												
<40	15	0.1	167	8.3	130	19.0	370	9.5	798	9.1	64	4.9
40-49	7,212	30.2	580	28.8	281	41.0	1,366	34.9	3,812	43.5	471	36.1
50-59	9,842	41.2	739	36.7	186	27.2	1,385	35.4	2,851	32.5	516	39.5
60+	6,793	28.5	530	26.3	88	12.8	793	20.3	1,311	14.9	254	19.5
Total	23,862		2,016		685		3,914		8,772		1,305	
Family history†												
No	21,031	88.1	1,698	84.2	605	88.3	3,326	85.0	7,346	83.7	1,044	80.0
Yes	2,831	11.9	318	15.8	80	11.7	588	15.0	1,426	16.3	261	20.0
Calcification												
No	23,862	100.0	1,737	86.2	589	86.0	3,029	77.4	5,357	61.1	619	47.4
Yes	0	0	279	13.8	96	14.0	885	22.6	3,415	38.9	686	52.6

* BBD, benign breast disease; PDWA, proliferative disease without atypia.

† Family history of breast cancer in a mother, sister, or daughter.

TABLE 4
Breast cancer incidence rates in the Breast Cancer Detection Demonstration Project study population

Classification	No. of subjects	Average age (years)	No. of cases	Crude rate*	Age-adjusted rate†
Normal subjects	23,862	55.0	169	216.5	206.5
Other benign breast disease	2,016	53.1	37	238.3	235.6
Fibroadenoma	685	48.2	17	308.2	334.3
Nonproliferative disease	3,914	51.5	93	304.0	309.8
Proliferative disease without atypia	8,772	50.1	271	394.7	413.0
Atypical hyperplasia	1,305	52.1	67	658.3	663.3
Total	40,554	53.3	654	313.6	308.9

* Annual rate/100,000 person-years.

† Adjusted for age 52.5 years with $\beta_{age} = 0.01891$.

the degree of epithelial abnormality increased, from nonproliferative disease to proliferative disease without atypia to atypical hyperplasia, breast cancer incidence increased. Women with atypical hyperplasia were the highest risk category, with an age-adjusted rate of 663.3 compared with the normal subjects.

Relative risks (RR) by benign breast disease type and family history and calcification are shown in table 5. While no significant elevation in risk was observed for women with other benign breast disease, women with nonproliferative disease, proliferative disease without atypia, and atypical hyperplasia displayed a progressively increasing risk for the development of breast cancer compared with normals, which was consistent with our belief that these represent more severe forms of benign breast disease. Women with fibroadenoma had a relative risk of 1.7, with a lower 95 per cent confidence limit of 1.0. Since no interactions were significant, the risks associated with combinations of factors can be predicted by multiplying the individual risks from table 5. For example, over all age groups, a woman with atypical hyperplasia, a positive family history, and the presence of calcification would have an estimated risk of 6.5 ($3.0 \times 1.8 \times 1.2$) times that of a woman without these risk factors. The assumption of proportional hazards seemed reasonable, as demonstrated by the proportional incidence curves shown in figure 1.

TABLE 5
Age-adjusted relative risk estimates of breast cancer obtained from the proportional hazards model in the Breast Cancer Detection Demonstration Project study population

Risk factor	Relative risk*	95% confidence interval
Other benign breast disease	1.2	0.8-1.7
Fibroadenoma	1.7	1.0-2.8
Nonproliferative disease	1.5	1.1-2.0
Proliferative disease without atypia	1.9	1.5-2.4
Atypical hyperplasia	3.0	2.1-4.1
Family history	1.8	1.5-2.1
Calcification	1.2	1.0-1.5

* The reference population for benign breast disease risk comparison is the normal cohort.

Tables 6-8 show the rates of breast cancer development in women with specific benign breast disease types stratified by age (table 6), family history (table 7), and calcification status (table 8). Regardless of which of the three stratification variables was selected, the pattern of increasing breast cancer rate with increasing severity of benign breast disease was apparent. For each of the stratification variables examined, atypical hyperplasia always had the highest rate.

The risk in women with atypical hyperplasia varied by age group (table 6) and was most pronounced in women under age 46 years, in whom the breast cancer incidence rate reached 710.5 (RR = 5.7, 95 per cent

Project study population

Crude rate*	Age-adjusted rate†
216.5	206.5
238.3	235.6
308.2	334.3
304.0	309.8
394.7	413.0
658.3	663.3
313.6	308.9

TABLE 5

Risk estimates of breast cancer
proportional hazards model in the
Breast Cancer Detection Demonstration Project study
population

	Relative risk*	95% confidence interval
Case	1.2	0.8-1.7
	1.7	1.0-2.8
	1.5	1.1-2.0
Throughout	1.9	1.5-2.4
	3.0	2.1-4.1
	1.8	1.5-2.1
	1.2	1.0-1.5

Population for benign breast disease
the normal cohort.

the rates of breast cancer in women with specific types stratified by age category (table 7), and calculated (table 8). Regardless of stratification variables, the pattern of increasing risk with increasing severity of disease was apparent. For stratification variables examined, atypical hyperplasia always had the

highest risk in women with atypical hyperplasia (table 6) and was highest in women under age 46. The breast cancer incidence rate in women with atypical hyperplasia was 710.5, 95 per cent

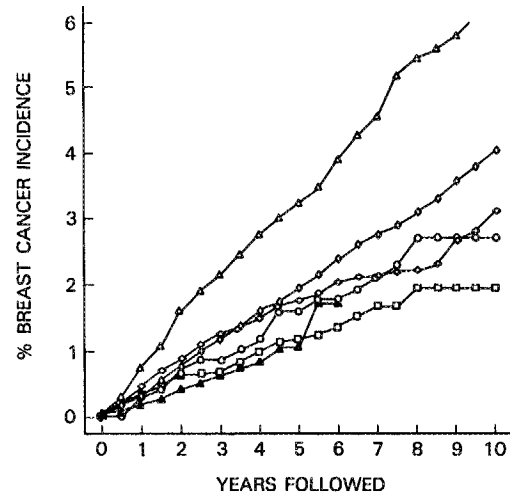


FIGURE 1. Breast cancer incidence in the Breast Cancer Detection Demonstration Project study population. Key: Δ , atypical hyperplasia; \diamond , proliferative disease without atypia; \circ , nonproliferative disease; \square , fibroadenoma; \blacksquare , other benign breast disease; \blacktriangle , normal subjects.

confidence interval 3.0-10.6) compared with normal subjects.

DISCUSSION

We conducted a prospective cohort study of 16,692 women in the Breast Cancer Detection Demonstration Project with biopsy-proven benign breast disease who were subsequently followed for over eight years for the development of breast cancer. Our results demonstrate that the risk of breast cancer development varies in women with benign breast disease and that risk increases as the degree of epithelial abnormality increases (table 5).

Our data indicate almost a sixfold increase in the rate of breast cancer in women under age 46 years with atypical hyperplasia compared with normal subjects (710.5 vs. 125.0, respectively) and over a twofold increase in the rate in women over 55 years

TABLE 6
Breast cancer incidence rates in the Breast Cancer Detection Demonstration Project study population, by age group

Age group* (years)	No. of subjects	Average age	No. of cases	Crude rate†
<46				
Normal subjects	3,395	43.1	14	125.0
Other BBD‡	500	40.8	10	252.2
Fibroadenoma	319	40.3	8	311.0
Nonproliferative disease	1,162	41.0	24	260.7
PDWA‡	2,926	41.3	79	337.7
Atypical hyperplasia	302	41.8	17	710.5
46-55				
Normal subjects	10,132	50.6	53	159.0
Other BBD	736	50.9	12	211.4
Fibroadenoma	224	50.4	4	223.8
Nonproliferative disease	1,509	50.5	34	287.6
PDWA	3,719	50.1	109	373.6
Atypical hyperplasia	596	50.5	28	594.5
>55				
Normal subjects	10,335	63.3	102	304.2
Other BBD	780	63.1	15	254.9
Fibroadenoma	142	62.2	5	432.3
Nonproliferative disease	1,243	62.4	35	366.1
PDWA	2,127	62.2	83	516.0
Atypical hyperplasia	407	62.1	22	715.3

* Age at time of entry biopsy.

† Annual rate/100,000 person-years.

‡ BBD, benign breast disease; PDWA, proliferative disease without atypia.

TABLE 7
Breast cancer incidence rates in the Breast Cancer Detection Demonstration Project study population, by family history

	No. of women	Average age (years)	No. of cases	Crude rate*	Age-adjusted rate†
Without family history					
Normal subjects	21,031	54.9	133	193.3	184.7
Other BBD‡	1,698	52.9	29	221.1	219.4
Fibroadenoma	605	48.2	15	306.4	332.4
Nonproliferative disease	3,326	51.2	67	256.6	263.0
PDWA‡	7,346	49.9	196	338.7	355.8
Atypical hyperplasia	1,044	52.1	51	622.3	627.0
With family history					
Normal subjects	2,831	56.2	36	388.1	361.9
Other BBD	318	54.4	8	332.3	320.6
Fibroadenoma	80	48.2	2	322.5	349.8
Nonproliferative disease	588	52.7	26	580.2	578.0
PDWA	1,426	50.9	75	694.7	716.0
Atypical hyperplasia	261	52.2	16	807.2	811.8

* Annual rate/100,000 person-years.

† Adjusted for age 52.5 years with $\beta_{age} = 0.01891$.

‡ BBD, benign breast disease; PDWA, proliferative disease without atypia.

TABLE 8
Breast cancer incidence rates in the Breast Cancer Detection Demonstration Project study population, by histologic presence of calcification

	No. of women	Average age (years)	No. of cases	Crude rate*	Age-adjusted rate†
Without calcification					
Normal subjects	23,862	55.0	169	216.5	206.5
Other BBD‡	1,737	52.8	32	240.5	239.1
Fibroadenoma	589	47.2	14	295.8	327.0
Nonproliferative disease	3,029	51.0	71	301.1	309.8
PDWA‡	5,357	49.3	141	339.8	361.0
Atypical hyperplasia	619	51.9	30	635.8	643.1
With calcification					
Normal subjects	0	NA‡	NA	NA	NA
Other BBD	279	55.2	5	225.3	214.1
Fibroadenoma	96	54.1	3	383.4	372.0
Nonproliferative disease	885	53.1	22	313.8	310.3
PDWA	3,415	51.4	130	478.6	488.7
Atypical hyperplasia	686	52.2	37	677.7	681.6

* Annual rate/100,000 person years.

† Adjusted for age 52.5 years with $\beta_{age} = 0.01891$.

‡ BBD, benign breast disease; PDWA, proliferative disease without atypia; NA, not applicable.

(table 6). The difference in risk for atypical hyperplasia by age is in agreement with an earlier study (3), which showed that atypical lobular hyperplasia specifically was associated with a sixfold increase in the relative risk of breast cancer among women aged 30-45 years, and with a threefold increase in risk in women aged 45 years or

older. Thus, the presence of atypical hyperplasia at an early age appears to be a particularly important prognostic sign for subsequent development of breast cancer. The higher risks for atypical lesions seen in younger women may be the result of a preponderance of familial breast cancers among younger women or of misdiagnosis

of lobular hyperplasia in young women (15). In our study, women with atypical hyperplasia have cancer at a shorter interval between diagnosis of hyperplasia and cancer than the controls, suggesting that the cancer is contributed by the hyperplasia and were not two of follicles. This conclusion is based on the hyperplasia in situ carcinoma.

We found that the incidence of breast cancer in women with atypical hyperplasia was significantly elevated compared with the normal subjects. The youngest women in these rates had the highest number of events. The results of this study show no increase in the incidence of adenoma with that of atypical hyperplasia that fibroadenoma perimenopausal periods represent.

In our study, the significant proportion of benign breast disease increased a twofold (1.2). Hutter et al. reported an increase in histologic evidence of benign breast disease (Page (11)) in the calcification study.

Women with atypical hyperplasia have an excess risk of developing a proliferative disease in women with atypical hyperplasia.

Using a case-control study of that of Page et al. in Wales, the incidence of benign breast disease increased with age and the increase in the incidence of hyperplasia

Project study population,

Crude rate*	Age-adjusted rate†
193.3	184.7
221.1	219.4
306.4	332.4
256.6	263.0
338.7	355.8
622.3	627.0
388.1	361.9
332.3	320.6
322.5	349.8
580.2	578.0
694.7	716.0
807.2	811.8

Project study population, by

Crude rate*	Age-adjusted rate†
216.5	206.5
240.5	239.1
295.8	327.0
301.1	309.8
339.8	361.0
635.8	643.1
NA	NA
225.3	214.1
383.4	372.0
313.8	310.3
478.6	488.7
677.7	681.6

, not applicable.

presence of atypical hyperplasia appears to be a paraprognostic sign for subsequent breast cancer. The atypical lesions seen in may be the result of a familial breast cancers or of misdiagnosis

of lobular carcinoma in situ as atypical hyperplasia, a condition often found in young women as opposed to older women (15). In our series, 10 women with atypical hyperplasia were subsequently reported to have cancer in situ. We examined the time interval between the diagnoses of atypical hyperplasia and cancer in situ and found that the cancer in situ diagnoses were distributed evenly over the follow-up period and were not clustered in the first year or two of follow-up. Hence, one may reasonably conclude that these 10 cases of atypical hyperplasia were not misdiagnosed cases of in situ carcinoma.

We found that breast cancer rates in women with fibroadenoma were appreciably elevated ($RR = 1.7$) over those in normal subjects, particularly in women in the youngest age group (table 6). However, these rates are based on a very small number of events. This result differs from the results of two recent studies (8, 10) in which no increase in risk for women with fibroadenoma was reported, but is in agreement with that of Moskowitz et al. (9), who found that fibroadenoma occurring during the perimenopausal and postmenopausal periods represented a significant risk marker.

In our study, calcification was a significant prognostic indicator in women with benign breast disease (table 8), but it increased a woman's risk only slightly ($RR = 1.2$). Hutchinson et al. (8) previously reported an excess risk associated with the histologic presence of calcification in the benign breast disease lesion. Dupont and Page (11) also found that the presence of calcification elevated the cancer risk in women with benign breast disease, but the excess risk was limited to women with proliferative disease and was of no importance in women with nonproliferative disease.

Using a classification system similar to that of Page et al. (16), Roberts et al. (10), in Wales, followed 326 biopsy-proven benign breast disease patients for almost 13 years and reported a two- to threefold increase in risk in women with atypical hyperplasia compared with the normal popu-

lation. Dupont and Page (11) followed a series of over 3,000 women for 17 years whose biopsies were reviewed using specifically defined criteria (16). They reported that the majority (70 per cent) of the women with benign breast disease whom they followed were not at increased risk for breast cancer. Women with proliferative disease without atypia were at a twofold increase in risk compared with women with nonproliferative lesions, and a fivefold increase in risk was associated with women with atypical hyperplasia compared with women with nonproliferative disease. Dupont and Page found the highest relative risk in women who had both atypical hyperplasia and a positive family history for breast cancer (11 times that in women who had nonproliferative disease).

Our study differs from that of Dupont and Page (11) in several ways. As mentioned earlier, benign breast disease slides in the present study were not centrally reviewed using a defined criterion and therefore may include diagnostic heterogeneity. This may be complicated by the fact that atypical hyperplasia has only recently been carefully characterized (3, 16) and is defined as having some of the histologic and cytologic features of in situ carcinoma. In our series, a broader definition of atypical hyperplasia than that which was used by Page et al. (16) must be presumed and probably accounts for the fact that 8 per cent of our benign breast disease women were reported to have atypical hyperplasia compared with only 4 per cent in the Dupont and Page series. One might expect to find lower relative risks associated with a broader definition of atypical hyperplasia, particularly since cases of cancer in situ were reported separately in this study. Moreover, the inclusion of misdiagnosed proliferative disease without atypia in the current series of women with atypical hyperplasia might further account for our finding of a lower relative risk for atypical hyperplasia.

Another important difference between our study and that of Dupont and Page is

the reference population. We report relative risks for the benign breast disease subtypes with the normal cohort as a reference, whereas Dupont and Page used the nonproliferative disease group. We investigated the appropriateness of using the normal cohort in the following ways. Follow-up on our normal subjects began six months after they had undergone a five-year screening phase, whereas follow-up on our subjects with benign breast disease began six months after their disease was detected; therefore, a bias could have been introduced because of either the asymmetrical start of follow-up or because our normal subjects consisted of a group from which women with breast cancer were intentionally excluded. To address the first issue, we reanalyzed the data starting everyone's follow-up at the time of the follow-up phase baseline exam; to address the second issue, we reanalyzed the data using only those women who developed benign breast disease during the screening phase, with the other benign breast disease group as the reference, since they represented the least severely affected benign breast disease subtype. In this second analysis, follow-up began six months after the diagnosis of benign breast disease. Neither of these anal-

yses is subject to a bias introduced by different starting points for follow-up, and, as table 9 shows, both demonstrate the increased relative risk associated with proliferative disease both with and without atypia. In both sets of analyses, the relative risk estimates were similar to those found in table 5. We interpret this to mean that neither the asymmetrical follow-up period nor the fact that our normal cohort went through five years of screening produced any appreciable bias in this study. In addition, we compared the age-adjusted rates in the first 60 months of follow-up with the rates for more than 60 months to further assess whether screening for breast cancer during the first five years of the study influenced the rate of breast cancer development. We found that the rates were comparable in all but the nonproliferative benign breast disease group, in which the rate decreased from 364.0 to 222.8 per 100,000 persons-years. This is reflected in the incidence curve shown in figure 1.

Finally, our series was substantially larger than that of the Dupont and Page (11) study, allowing us to examine potential effects in subgroups in greater detail. Having large numbers of observations in each of the benign breast disease subtypes al-

lowed us to associated w Dupont and women with at a significant

While the suggest that benign breast interpreted in weaknesses a sign. To our study of benign date. It is pr follow-up was distribution However, the lected in ove throughout t utes to a ma center patho form showing central patho ducted only c presence of indicating be data may ref agnoses of be dom misclass ease types sh mate of the proliferative nally, genera be somewhat on predomin slightly bette for this age gr

We conclu breast cancer disease incre lial abnormal type of benign highest risk i perplasia and breast cancer

TABLE 9

Comparison of age-adjusted relative risk estimates of breast cancer using different reference populations, Breast Cancer Detection Demonstration Project study population

Risk factor	Reference group A*		Reference group B†	
	Relative risk	95% confidence interval	Relative risk	95% confidence interval
Normal subjects	1.0			
Other benign breast disease	0.9	0.5-1.5	1.0	
Fibroadenoma	1.7	0.8-3.5	1.4	0.8-2.5
Nonproliferative disease	1.0	0.7-1.5	1.3	0.9-1.9
Proliferative disease without atypia	1.5	1.1-1.9	1.6	1.2-2.3
Atypical hyperplasia	2.2	1.4-3.4	2.5	1.7-3.8
Family history	1.9	1.5-2.4	1.9	1.5-2.3
Calcification	1.3	1.0-1.8	1.2	1.0-1.5

* The reference population is the normal cohort. Follow-up begins at the time of the follow-up phase baseline exam for all study subjects. Number of cases is 349 from a total of 39,931 women.

† The reference population is the other benign breast disease group. Analysis is based on only those women who developed benign breast disease during the screening phase. Number of cases is 485 from a total of 16,692 women.

a bias introduced by points for follow-up, and, both demonstrate the risk associated with pro- both with and without of analyses, the relative similar to those found interpret this to mean that metrical follow-up period our normal cohort went of screening produced as in this study. In addi- the age-adjusted rates in s of follow-up with the n 60 months to further eening for breast cancer e years of the study in- f breast cancer develop- at the rates were com- he nonproliferative be- group, in which the rate 4.0 to 222.8 per 100,000 s is reflected in the in- n in figure 1.

ries was substantially t the Dupont and Page us to examine potential s in greater detail. Hav- of observations in each st disease subtypes al-

reference populations, Breast on

Reference group B†	
Relative risk	95% confidence interval
1.0	
1.4	0.8-2.5
1.3	0.9-1.9
1.6	1.2-2.3
2.5	1.7-3.8
1.9	1.5-2.3
1.2	1.0-1.5

the follow-up phase baseline

s based on only those women is 485 from a total of 16,692

lowed us to identify the increased risks associated with most of these subtypes; Dupont and Page, however, identified only women with proliferative disease as being at a significantly increased risk.

While the results reported here strongly suggest that breast cancer risk varies by benign breast disease type, they must be interpreted in the light of the strengths and weaknesses associated with the study design. To our knowledge, this is the largest study of benign breast disease reported to date. It is prospective in nature, excellent follow-up was achieved, and the geographic distribution of its participants was wide. However, the fact that these data were collected in over 29 project centers scattered throughout the United States also contributes to a major study weakness: Although center pathologists completed a standard form showing the results of each biopsy, central pathologic confirmation was conducted only on biopsies that indicated the presence of breast cancer, not on those indicating benign breast disease. Thus, our data may reflect inconsistencies in the diagnoses of benign breast lesions. Such random misclassification of benign breast disease types should result in an underestimation of the true risk associated with proliferative and/or atypical lesions. Finally, generalization of these results may be somewhat limited because our data are on predominantly white women who are slightly better educated than the average for this age group in the United States (13).

We conclude that the risk of developing breast cancer in women with benign breast disease increases with the degree of epithelial abnormality associated with the specific type of benign breast disease and that the highest risk is in women with atypical hyperplasia and a positive family history for breast cancer.

REFERENCES

- Veronesi U, Pizzocaro G. Breast cancer in women subsequent to cystic disease of the breast. *Surg Gynecol Obstet* 1968;126:529-32.
- Black MM, Barclay THC, Cutler SJ, et al. Association of atypical characteristics of benign breast lesions with subsequent risk of breast cancer. *Cancer* 1972;29:338-43.
- Page DL, Vander Zwaag R, Rogers LW, et al. Relation between component parts of fibrocystic disease complex and breast cancer. *JNCI* 1978;61:1055-63.
- Kodlin D, Winger E, Morgenstern NL, et al. Chronic mastopathy and breast cancer: a follow-up study. *Cancer* 1977;39:2603-7.
- Donnelly PK, Baker K, Carney JD, et al. Benign breast lesions and subsequent breast carcinoma in Rochester, Minnesota. *Mayo Clin Proc* 1975;50:650-6.
- Monson RR, Yen S, MacMahon B, et al. Chronic mastitis and carcinoma of the breast. *Lancet* 1976;2:224-6.
- Coombs LJ, Lilienfeld AM, Bross IDJ, et al. A prospective study of the relationship between benign breast disease and breast carcinoma. *Prev Med* 1979;8:40-52.
- Hutchinson WB, Thomas DB, Hamlin WB, et al. Risk of breast cancer in women with benign breast disease. *JNCI* 1980;1:13-20.
- Moskowitz M, Gartside P, Wirman JA, et al. Proliferative disorders of the breast as risk factors for breast cancer in a self-selected screened population: pathologic markers. *Radiology* 1980;134:289-91.
- Roberts MM, Jones V, Elton RA, et al. Risk of breast cancer in women with history of benign disease of the breast. *Br Med J* 1984;288:275-8.
- Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. *N Engl J Med* 1985;312:146-51.
- Baker LH, Chin TDY, Wagner KV. Progress in screening for early breast cancer. *J Surg Oncol* 1985;30:96-102.
- Baker LH. Breast cancer detection demonstration project: five-year summary report. *CA* 1982;4:194-230.
- National Institutes of Health, National Cancer Institute. Cancer incidence and mortality in the United States: SEER 1973-1981. Bethesda, MD: National Institutes of Health, 1985. (NIH publication no. 85-1837).
- Ackerman LV, Katzenstein AL. The concept of minimal breast cancer and the pathologist's role in the diagnosis of "early carcinoma." *Cancer* 1977;39:2755-63.
- Page DI, Dupont WD, Rogers LW, et al. Atypical hyperplastic lesions of the female breast: a long-term follow-up study. *Cancer* 1985;55:2698-2708.